Conferences and Reviews

Anticoagulation and Atrial Fibrillation

Putting the Results of Clinical Trials Into Practice

Discussant
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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Dawn E. DeWitt, MD, Chief Medical Resident, Henry Rosen, MD, Professor and Associate Chair, and Paul G. Ramsey, MD, Professor and Chair of the Department of Medicine.

The thromboembolic risk of atrial fibrillation varies with the underlying cause, associated heart disease, and history of previous embolism. Decisions regarding warfarin anticoagulation therapy require a careful assessment of relative risks of thromboembolism and bleeding. Anticoagulation is strongly indicated for valvular atrial fibrillation and to prevent recurrent stroke in patients with atrial fibrillation and previous stroke or transient ischemic attack. Several randomized trials have consistently shown a reduction of the risk with the use of warfarin in nonvalvular atrial fibrillation, and anticoagulation is recommended. With a careful selection of patients, the risk of major bleeding on warfarin therapy is 2% to 4% per year. Aspirin therapy is less efficacious but also less risky than warfarin. Patients younger than 60 with lone atrial fibrillation do not require anticoagulation.

(Wipf JE: Anticoagulation and atrial fibrillation—Putting the results of clinical trials into practice. West J Med 1995; 163:145-152)

Case Summary

The patient is a 74-year-old man with a history of diabetes mellitus, hypertension, and congestive heart failure in whom chronic atrial fibrillation developed. After anticoagulation, he was admitted for elective cardioversion. On examination, he was without murmur or congestive heart failure. An electrocardiogram showed atrial fibrillation and an old, silent, anterior-wall myocardial infarction. By echocardiography, the left atrial size was 4.8 cm, and no valvular disease or thrombi were seen. The patient did not convert to sinus rhythm with the administration of quinidine sulfate, and frequent ventricular pauses developed, requiring discontinuation of the drug. Electrocardioversion was not attempted. Ongoing warfarin sodium anticoagulation was continued. Four months later, the patient was admitted with an embolus of the right iliac artery. At this time, a prothrombin time (PT) international normalized ratio (INR) was subtherapeutic at 1.4.

Problems

This case poses a number of challenging questions in the management of atrial fibrillation and the prevention of thromboembolic complications. Addressing the following should help to clarify therapy:

- What is the cause of atrial fibrillation?
- What is the risk of thromboembolism, especially to the brain?
- Can the risk of thromboembolism be reduced by warfarin therapy?
- How great is the risk of hemorrhage on warfarin therapy?
- Is the use of aspirin a reasonable alternative?

Many physicians have faced similar questions with other patients. Like this clinical case, many cases have unique elements that make management difficult. Although it may be tempting to defer complex management decisions to cardiologists or neurologists, primary physicians are often best able to assess patients' level of cognitive and physical function and suitability for anticoagulation. Because long-term anticoagulation therapy is frequently managed by primary care providers, familiarity with indications for the use of warfarin in patients with atrial fibrillation allows clinicians to be actively involved in decisions to initiate and maintain anticoagulation therapy.*

*See also the editorial by S. R. Stratton, MD, "Warfarin Sodium or Aspirin Therapy to Prevent Stroke in Nonrheumatic Atrial Fibrillation," on pages 177-179 of this issue.

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ABBREVIATIONS USED IN TEXT

AFASAK = Atrial Fibrillation, Aspirin, Anticoagulation Study of Copenhagen
BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation
CAFA = Canadian Atrial Fibrillation Anticoagulation [study]
INR = international normalized ratio
ISI = international sensitivity index
PT = prothrombin time
PTR = prothrombin time ratio
SPAF I, II = Stroke Prevention in Atrial Fibrillation [studies] I and II
SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation [study]

Factors That Predispose to Atrial Fibrillation

The most prevalent cause of atrial fibrillation has historically been rheumatic valvular heart disease, predominantly mitral stenosis. The connection between atrial fibrillation and mitral valve disease was first made in the 1700s by Jean Baptiste de Senac (1693 to 1770), physician to King Louis XV, who published the first text on cardiology.[1] He correlated an irregular pulse and palpitations with autopsy observations of mitral valve disease. At the turn of the 20th century, Sir James Mackenzie found that the a wave of the jugular pulse was caused by atrial contraction and therefore was lost in atrial fibrillation.[2]

In the United States, where rheumatic heart disease is uncommon, the cause of atrial fibrillation is usually nonvalvular heart disease, principally atherosclerotic cardiovascular disease. The patient in the case reviewed here has typical nonvalvular atrial fibrillation with congestive heart failure, coronary artery disease, and hypertension. The prevalence of various conditions in atrial fibrillation and the prevalence of atrial fibrillation in each condition are shown in Table 1.[3] The prevalence of atrial fibrillation is low in patients with angina, but about 10% of patients will have it transiently after coronary artery bypass grafting or myocardial infarction. It is present in nearly half of patients with mitral stenosis and 75% of patients with mitral regurgitation requiring valve replacement. Isolated aortic valve disease is associated with atrial fibrillation in only 1% of cases.[4] It is infrequent in cases of acute pericarditis, but common in chronic pericardial constriction. Of patients with thyrotoxicosis, 10% to 20% have atrial fibrillation, and a third will have persistence of their arrhythmia after the treatment of hyperthyroidism.

Atrial Fibrillation and Thromboembolism

Atrial fibrillation is currently the cause of nearly half of cardiogenic embolic events.[5,6] An estimated 2% to 4% of adults, or 1.5 to 2 million Americans, have atrial fibrillation, with a great effect on the incidence of stroke. Of patients presenting with acute stroke, 15% to 25% are in atrial fibrillation.

Emboli of cardiac origin are less commonly associated with rheumatic heart disease, acute myocardial infarction, or prosthetic valves. Most clinically recognized cardiac emboli are cerebral, with only a third at systemic sites, such as the extremities, as in the patient presented here. The kidneys and the spleen are also relatively common sites of embolism.

Thrombi as small as 3 to 4 mm are reported to cause strokes. Because a quarter of strokes in patients with atrial fibrillation are nonembolic, there may be other mechanisms by which thrombi cause stroke.

Confirming the clinical diagnosis of cardioembolic stroke is difficult. There are no universally agreed-on criteria, and individual features are neither sensitive nor specific. Suggestive features that distinguish a stroke due to cardiogenic emboli from a carotid artery source include the knowledge of a possible cardiogenic source, a maximal deficit at its onset, a large infarct, or infarcts occurring in more than one vascular distribution.[6] Hemorrhagic transformation may be seen in patients with embolic strokes following reperfusion of the stroke area after breakup of the embolism. The presence of a cardiogenic source in the absence of cerebrovascular disease is most suggestive of the diagnosis.

The risk of thromboembolic events, most of which are strokes, is known from several epidemiologic studies of atrial fibrillation. The Framingham Heart Study, which monitored 5,200 residents of Framingham, Massachusetts, for the development of cardiovascular disease, found a high risk of stroke in those with valvular atrial fibrillation, 17.6 times greater than in controls, with the patients' mean age being 60 years.[7] The risk of stroke in patients with nonvalvular atrial fibrillation, with a mean age of 70 years, was 5% per year, or 5.6-fold higher than in controls. The increased incidence of thromboembolism

TABLE 1.—*Diseases Associated With Atrial Fibrillation**

Disease	*Prevalence in Patients With Atrial Fibrillation, %*	*Prevalence of Atrial Fibrillation in Each Disease, %*
Valvular heart disease		
Rheumatic valvular disease	20-30	20
Nonvalvular heart disease		
Coronary artery disease	50-60	1
Hypertension	40-60	5-10
Acute myocardial infarction	<5	5-15
After coronary bypass surgery (transient)	<5	30-40
Congestive cardiomyopathy	<1	20
Hypertrophic cardiomyopathy	<1	10
Acute pericarditis	<1	5
Pericardial constriction	<1	35
Alcohol (holiday heart syndrome)	<1	40
Conductive system disease (sick sinus syndrome, Wolff-Parkinson-White syndrome)	<5	<5
Hyperthyroidism	2.5	20-30
Lone atrial fibrillation	10	--
Pulmonary embolism	<1	3

*Modified from Albers et al,[3] with permission from the *Annals of Internal Medicine*.

in nonvalvular atrial fibrillation has been confirmed in other studies, with rates five to seven times those in controls.[8,9] Clearly underlying cardiovascular disease is an important factor in determining the risk of stroke from atrial fibrillation.

Trials of Anticoagulation in Nonvalvular Atrial Fibrillation

Several recently reported randomized trials of anticoagulation in nonvalvular atrial fibrillation show the efficacy of using warfarin.[10-15] To interpret the anticoagulation intensity of each trial and compare studies of warfarin bleeding risk, the relationship between the prothrombin time ratio (PTR) and the INR must be understood. The PTR is a patient's PT over the PT from batched controls. The INR is derived from the PTR on a specially designed nomogram for a given international sensitivity index (ISI), which is provided by the manufacturer for each shipment of thromboplastin reagent and varies in different laboratories. For example, an INR range of 2.0 to 3.0 corresponds to a PTR range of 1.5 to 1.8 when the ISI is 1.8 and a PTR of 1.4 to 1.6 when the ISI is 2.3.[16] The INR is not more accurate than the PTR as it is derived from the PTR, but the INR allows a comparison of prothrombin times from different laboratories. In the Northwest, about 70% of clinical laboratories use the INR measurement, compared with 50% or less across the country.

The published randomized trials in nonvalvular atrial fibrillation are the Atrial Fibrillation, Aspirin, Anticoagulation study (AFASAK), reported in 1989 from Copenhagen; the Stroke Prevention in Atrial Fibrillation studies (SPAF I and II) and the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF), which are multicenter American trials; the Canadian Atrial Fibrillation Anticoagulation study (CAFA), a multicenter Canadian trial; and the Stroke Prevention in Nonrheumatic Atrial Fibrillation study (SPINAF), a Veterans Affairs cooperative trial.[10-15] In all, about 3,000 patients were enrolled in these trials.

One of the problems in generalizing results from the trials to clinical practice is that more than 90% of screened patients were excluded from the studies. Enrolled patients included elderly patients (older than 75), persons with either sustained or intermittent atrial fibrillation, and those with atrial fibrillation of long duration or of recent onset. Left atrial size was not a criterion for enrollment. Criteria for patient exclusion included, but were not limited to, mitral stenosis, a requirement or contraindication for either warfarin or aspirin therapy, high bleeding risk, recent stroke, recent transient ischemic attack, or the presence of emboli. Risk factors for bleeding that resulted in a patient's exclusion were active peptic ulcer, bleeding disorder, previous hemorrhage, occult bleeding, uncontrolled hypertension, severe renal or hepatic disease, dementia, gait disorder, and alcoholism.

The highest intensities of anticoagulation were in the AFASAK and SPAF studies, with INR ranges of 2.8 to 4.2 and 2.0 to 4.5, respectively. The other trials more closely approximated an INR range of 2.0 to 3.0 currently recommended for atrial fibrillation. Two trials had a randomized arm of aspirin therapy—AFASAK, with a dose of 75 mg aspirin per day, and SPAF, 325 mg of aspirin per day. (SPAF II was a continuation of SPAF I after the placebo arm was dropped, and those patients were randomly reassigned to receive aspirin, 325 mg, or warfarin.) Patients in the control arm of the BAATAF trial were allowed to take aspirin, and 46% took aspirin regularly, most at 325 mg per day. The aspirin data are discussed in detail later.

The incidence of central nervous system events in patients treated with warfarin and in controls taking a placebo on an intention-to-treat analysis is graphed in Figure 1.[10-14] Transient ischemic attacks are excluded, and all stroke events had a persistence of neurologic deficits of longer than 24 hours. All five trials consistently showed a similar magnitude of benefit of using warfarin over placebo, for an overall significant stroke risk reduction of 70%. In the AFASAK study, all but one of the stroke events occurred in patients with subtherapeutic INR values. All trials were stopped prematurely when an interim analysis showed substantial warfarin benefit, or in the case of CAFA, a trend toward warfarin benefit and the other trial results were known. The annual incidence of noncerebral systemic emboli was also reduced by warfarin therapy in each trial. The overall reduction in the incidence of systemic thromboembolism was 81%, statistically insignificant because so few events occurred overall.[17,18]

Bleeding Complications of Warfarin Therapy

Warfarin sodium therapy is highly efficacious in reducing stroke in patients with atrial fibrillation, but it carries a hemorrhagic risk. Each trial had a different definition of major bleeding, but events included were se-

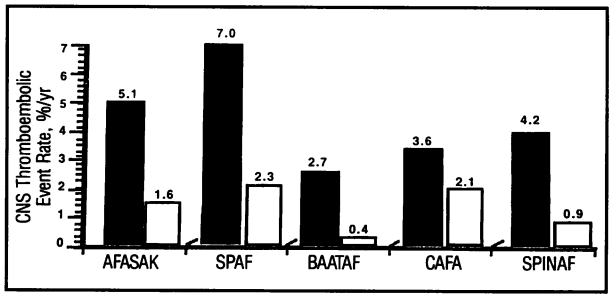

Figure 1.—The efficacy of the use of warfarin sodium is compared with that of placebo control in 5 prospective, randomized trials of nonvalvular atrial fibrillation. The annual incidence of central nervous system (CNS) events, excluding transient ischemia attacks, is shown for control (**dark bars**) and warfarin (**light bars**) arms of each study. AFASAK = Atrial Fibrillation, Aspirin, Anticoagulation study of Copenhagen; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation study; CAFA = Canadian Atrial Fibrillation Anticoagulation study; SPAF = Stroke Prevention in Atrial Fibrillation study; SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation study

vere and often life-threatening. For example, major bleeding in the BAATAF study was defined as intracerebral, fatal, or requiring transfusion of four or more units of blood products within 48 hours.[12] The rates of major bleeding in the nonvalvular atrial fibrillation trials were low, all 1.5% or less per year, with the exception of SPAF. The other trials had annual rates of 0.8% to 1.5% and 0.3% to 0.9% in the warfarin and placebo arms, respectively. In SPAF I, the trial with the highest INR intensity range, major hemorrhage occurred in 1.5% per year of those on warfarin therapy and 1.6% per year of those on placebo or aspirin therapy. The SPAF II trial had annual rates of 4.2% and 1.6% per year for patients on warfarin and aspirin therapy, respectively, in patients older than 75. How do these rates of bleeding compare with data on warfarin anticoagulation in unselected patients?

A recent multicenter study determined bleeding rates in 928 "unselected" consecutive patients observed in an anticoagulation clinic (distinct from trials just reviewed) (Figure 2).[19] The mean age at the start of the study was 57 years. Serious bleeding was defined as any bleeding that prompted a workup, such as cystoscopy, or that required no more than two units of blood transfused. Life-threatening bleeding included that leading to irreversible sequelae, cardiopulmonary arrest, surgical intervention or angiography, hypotension, transfusion of at least three units, or a hematocrit of 0.20 (20%) or less. Fatal bleeding was defined as that leading directly to a patient's death.

The cumulative incidence of serious bleeding was high, and bleeding occurred in 12% of patients during the first year of anticoagulation. After eight years, 40% of patients had had at least one episode of serious bleeding. The risk of life-threatening or intracranial bleeding was low, however, being 1.6% per year, and fatal bleeding occurred in four patients (0.4%), corresponding to the bleeding rates in the randomized atrial fibrillation trials. These rates are also comparable to several other recent studies of warfarin anticoagulation intensity in an INR range of 2 to 3. In a carefully selected group with close

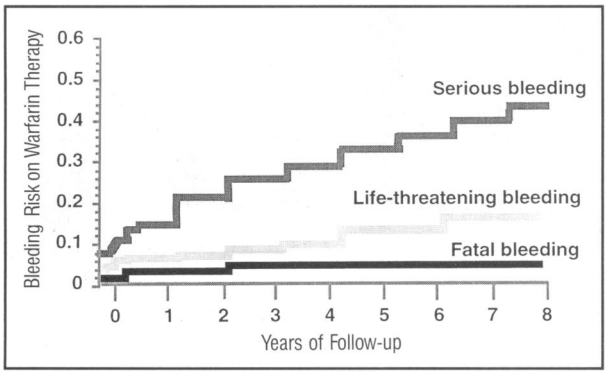

Figure 2.—In 928 unselected, consecutive patients on warfarin therapy who were observed in an anticoagulation clinic, the cumulative incidence of bleeding was high, but most events were not life-threatening. The graph shows rates of serious, life-threatening, and fatal bleeding (severity defined in text) over 8 years of follow-up (adapted from Fihn et al,[19] with permission).

monitoring, life-threatening and fatal bleeding events are uncommon. Earlier studies reporting major bleeding rates as high as 10% to 15% per year used greater intensities of anticoagulation and included agents other than warfarin.[20]

Older age has traditionally been considered a risk factor for bleeding and a relative contraindication for anticoagulation for that reason. Most clinicians are reluctant to anticoagulate elderly patients, yet this is the age group in whom thromboembolic complications with atrial fibrillation are most likely to develop. The Framingham study found an annual thromboembolic risk of 4.9% in patients aged 70 to 79 years and 7.1% in those aged 80 and older.[7]

The data on age alone as a risk factor for bleeding while on anticoagulation therapy are conflicting. Prospective and retrospective data on warfarin-related bleeding, broken down by age categories after adjustment for other known risk factors, showed that the risk did not increase stepwise with age older than 50, and confidence intervals were overlapping.[19] A recent Dutch study, however, suggested that age alone is a risk factor.[21] Certainly in older patients, the risk of falls and the ability to comply with therapy need to be carefully assessed before long-term warfarin anticoagulation is initiated.

Risk factors that definitely increase the incidence of hemorrhagic complications of warfarin therapy include a higher intensity of anticoagulation, recently initiated treatment (due to dose adjustment and possible overanticoagulation), an underlying anatomic lesion, and a previous episode of bleeding, particularly in the gastrointestinal tract. Those that probably contribute to a bleeding risk include hypertension, a history of stroke, alcohol abuse, and variability (instability) of the PTR, requiring frequent dose adjustments. Conditions reported to increase the incidence of bleeding (but which are not supported by most data) are female sex, smoking, diabetes mellitus, atrial fibrillation, and congestive heart failure.

Aspirin Therapy in Atrial Fibrillation

The randomized trials establish the efficacy of warfarin therapy in reducing the stroke risk of atrial fibrillation. What about aspirin therapy as an alternative? The annual rates of thromboembolic events for each of the trials with a randomized arm of aspirin are shown in Figure 3.[10,11,15] In the AFASAK study, taking 75 mg of aspirin per day did not confer benefit over taking a placebo, with each arm having an annual stroke incidence of 5.5% per year. The SPAF I and II trials both showed a reduction in the incidence of stroke events with a regimen of 325 mg of aspirin a day in patients younger than 75 years, with less benefit in those older than 75. In SPAF II, a regimen of 325 mg of aspirin a day was less efficacious than the use of warfarin, but was associated with less bleeding. In patients older than 75 in the SPAF II trial, the incidence of stroke with notable residual effects (ischemic or hemorrhagic) was 4.3% per year with aspirin therapy and 4.6% per year with warfarin therapy.[15] Despite close monitoring, the SPAF II study showed a clear increase in the

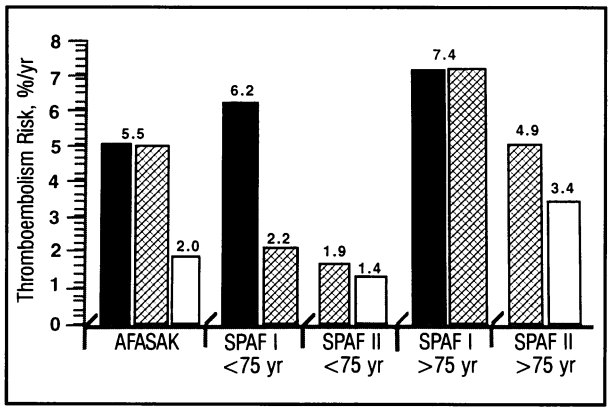

Figure 3.—The annual risk of thromboembolism occurring on aspirin therapy is shown for the control arm (**dark bars**), patients receiving aspirin (**hatched bars**), and those receiving warfarin sodium (**white bars**) for each randomized trial of aspirin therapy in patients with nonvalvular atrial fibrillation. The daily aspirin dose was 325 mg in each study except the Atrial Fibrillation, Aspirin, Anticoagulation study of Copenhagen (AFASAK), in which the dose was 75 mg. Warfarin had greater efficacy than aspirin in all studies, with aspirin of some benefit in the Stroke Prevention in Atrial Fibrillation studies (SPAF) of patients <75 years.

risk of all major hemorrhages in the older age group. As noted earlier, bleeding rates in SPAF II were greater than in the other trials and the intensity of anticoagulation higher than currently recommended. Aspirin taken by patients in the control group of the BAATAF study was not beneficial. Although the benefit from aspirin is debated, the data for the use of warfarin in patients with atrial fibrillation are currently more convincing than those for the use of aspirin.

To summarize, all the randomized trials showed efficacy of warfarin therapy in lowering the stroke risk of nonvalvular atrial fibrillation. Carefully monitored patients have a low risk of major bleeding (2% to 4% per year) on warfarin therapy, although it is possible that more intensive anticoagulation in older patients is associated with a greater bleeding risk. Practice guidelines by the Third American College of Chest Physicians Conference in 1992 strongly recommend long-term warfarin therapy for patients with nonvalvular atrial fibrillation, with the intensity of anticoagulation in the INR range of 2.0 to 3.0.[22] In older patients, the benefits of warfarin need to be balanced with a possibly greater bleeding risk.[23] The use of aspirin in a 325-mg-a-day dose is indicated principally for patients who are poor candidates for warfarin anticoagulation.

Anticoagulation in Valvular Atrial Fibrillation

Valvular heart disease is associated with a greatly increased risk of thromboembolism, and warfarin therapy reduces this risk, although there have been no randomized trials.[24,25] Mitral stenosis is the primary lesion associated with embolism, and the risk increases sevenfold if atrial fibrillation is present. The use of warfarin is strongly recommended in all patients with valvular atrial fibrillation, regardless of whether the fibrillation is chronic or intermittent, in the INR intensity range of 2.0 to 3.0.[26] For those with prosthetic valve replacement, a higher intensity of INR of 2.5 to 3.5 is recommended for mechanical valves. Patients with tissue valves should be anticoagulated with an intensity of 2.0 to 3.0.

Lone Atrial Fibrillation

A subset of patients with atrial fibrillation are known to do well without anticoagulation. The term "lone atrial fibrillation" was coined in 1954 for those without cardiovascular disease or hyperthyroidism.[27] In a Mayo Clinic (Rochester, Minnesota) study of lone atrial fibrillation spanning 30 years, 97% of all cases of atrial fibrillation were excluded.[28] Three fourths of the patients had intermittent atrial fibrillation. Patients were all younger than 60 years (mean age, 44) and carefully selected to exclude any associated medical conditions, such as cardiac or pulmonary disease, treated hypertension, or diabetes. After 15 years, a stroke had developed in only 1.3%, for an annual rate of 0.4%.

The low risk of lone atrial fibrillation was confirmed in two other studies, with mean ages of about 55 years and all patients in chronic atrial fibrillation, having event rates of 0% to 0.2% per year.[9,29] Patients reported to have lone atrial fibrillation in the Framingham study had a 2.6% annual risk of thromboembolic events, but their mean age was 70 years and about a third had hypertension[30]; most would have been excluded by the Mayo Clinic criteria. Lone atrial fibrillation, when carefully defined as atrial fibrillation in patients younger than 60 without systemic or cardiovascular disease, accounts for 5% or less of all cases of atrial fibrillation. The risk of thromboembolic events is less than 0.5% per year, and anticoagulation is not indicated for such cases, whether intermittent or constant, in patients younger than 60. For the uncommon circumstance where an elderly person meets the criteria for lone atrial fibrillation, optimal management is unknown. The annual stroke risk is 2.1% in subjects aged 70 to 79 years diagnosed with lone atrial fibrillation.[31]

Intermittent Atrial Fibrillation

Intermittent atrial fibrillation includes paroxysmal atrial fibrillation of sudden onset lasting a few hours and that persisting for a few days intermittently. The prospective data come from the SPAF I and BAATAF trials, with 34% and 17% of total patients in intermittent atrial fibrillation, respectively (combined 435 patient-years of observation).[12,13] The SPAF study found annual thromboembolic rates of 2.3% in those on warfarin therapy and 7.4% for those on placebo, no different from the rates in patients with chronic atrial fibrillation. The patients with intermittent atrial fibrillation in the BAATAF study had a thromboembolic rate of 1.3% per year, compared with 1.6% in patients with chronic atrial fibrillation, but there were few embolic events overall.

Retrospective studies of intermittent atrial fibrillation have shown a thromboembolic risk of 2% per year during

1,026 patient-years of observation.[32,33] The risk in the largest study was 6.8% in the first month of intermittent atrial fibrillation, but then decreased to 2% annually thereafter, unless chronic atrial fibrillation developed, when the risk increased to 5% per year.[32]

Another retrospective study found a 5% annual risk of thromboembolic events in 431 patient-years observed.[34] Mortality data from an insurance cohort found that the incidence of paroxysmal atrial fibrillation increased twofold in mortality compared with that in sinus rhythm controls, but less than in patients with chronic atrial fibrillation who had a sevenfold higher mortality than controls.[35] Because the risk of intermittent atrial fibrillation appears greater than that for sinus rhythm, these patients should be considered for anticoagulation, particularly those who remain in fibrillation for several days at a time.

Recurrent Stroke in Atrial Fibrillation

Atrial fibrillation is associated with a high risk of recurrent stroke, with the greatest risk being shortly after its onset. Between 15% and 30% of patients will have a recurrent stroke in the first year, and the lifetime risk is 30% to 75%, with the highest risk being for valvular atrial fibrillation.[6,36] A third of recurrent strokes are nonembolic.[37]

In a recent European multicenter trial, 1,007 patients with atrial fibrillation with a history of transient ischemic attack or minor ischemic stroke in the previous three months were randomly assigned to take warfarin sodium, 300 mg of aspirin, or placebo.[38] The annual incidence of stroke was significantly reduced from 12% in the placebo group to 4% in the group taking warfarin. Aspirin had no notable benefit over placebo. The annual rates of the incidence of major bleeding were 2.9% with warfarin therapy, 0.9% with aspirin therapy, and 0.7% with placebo. Nonrandomized studies also suggest that the use of warfarin is beneficial in preventing recurrent stroke in patients with atrial fibrillation who have had a stroke.[6] The recommended anticoagulation intensity for patients with atrial fibrillation and stroke is an INR of 2.0 to 3.0, with higher levels of 2.5 to 3.5 for those in whom a stroke develops while they are on lower intensity anticoagulation.[12]

Management of Newly Recognized Atrial Fibrillation

All patients with newly recognized atrial fibrillation must be evaluated for associated hyperthyroidism. Elderly patients may present with "apathetic hyperthyroidism," with atrial fibrillation as the only apparent clinical feature. Echocardiography is useful to detect valvular heart disease and evidence of silent coronary artery disease, such as infarcts and impaired left ventricular function. Despite extensive data about individual left atrial variables, no single measurement consistently predicts successful cardioversion or the maintenance of sinus rhythm after cardioversion. Left atrial enlargement should not preclude attempts at cardioversion.

The presence of thrombi in the atria or left atrial appendage is helpful in making anticoagulation decisions, but transthoracic two-dimensional echocardiography is poor at detecting atrial thrombi. Transesophageal echocardiography is far more accurate in detecting thrombi, because the esophageal view allows better visualization of the posterior aspects of the valves and atrial chambers. Transesophageal echocardiography is a costly endoscopic procedure, however, requiring close observation, and it is not recommended for the routine evaluation of atrial fibrillation and stroke.

Cardioversion of Atrial Fibrillation

The risk of embolism in cardioversion of atrial fibrillation without anticoagulation is 1% to 5%, and it is reduced to less than 1% with anticoagulation.[22,39-41] Emboli have been reported as long as ten days after cardioversion. Transesophageal echocardiography with the administration of heparin has been proposed before cardioversion to rule out thrombi and to avoid the need for warfarin before cardioversion.[42] The procedure is expensive, however, and safety has not yet been established in controlled trials. Cardioversion itself may precipitate embolic events, regardless of the presence or absence of an atrial thrombus on transesophageal echocardiography before the cardioversion.[43]

Because atrial activity may not return to normal immediately or for several weeks after sinus rhythm is restored, patients would still be at risk after cardioversion without warfarin therapy. Screening with transesophageal echocardiography is not an acceptable substitute for warfarin anticoagulation before cardioversion. Warfarin anticoagulation is recommended before and after cardioversion for stable patients with atrial fibrillation present longer than 48 hours.[44,45]

The use of antiarrhythmic agents improves the likelihood of successfully maintaining sinus rhythm after cardioversion. A meta-analysis of pooled results from randomized, controlled trials of quinidine in patients with atrial fibrillation showed that 69% of patients were in normal sinus rhythm three months after cardioversion, compared with 45% of those taking placebo.[46] By six months, sinus rhythm persisted in 58% and 33% of those treated with quinidine and placebo, respectively. At 12 months, 50% of the group taking quinidine were still in sinus rhythm, compared with only 5% of the placebo group. The mortality odds ratio of quinidine was 2.98, however. Sotalol hydrochloride, a β-blocker with antiarrhythmic properties, and low-dose amiodarone appear to have lower mortality profiles than other agents.[47-49] Concern about increased mortality with antiarrhythmic drugs has led many clinicians to discontinue them short term after cardioversion and to observe the patient for recurrence. In patients who tolerate atrial fibrillation poorly, long-term antiarrhythmic therapy after cardioversion is indicated.

Clinical Strategies

Based on the literature on atrial fibrillation and study results reviewed, clinical strategies can be developed for managing patients (Figures 4 and 5).[44] Absolute contraindications to anticoagulation include an underlying

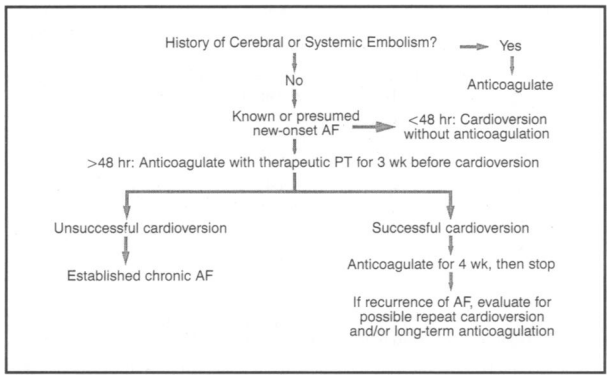

Figure 4.—Therapy for newly recognized atrial fibrillation (AF) requires assessing for previous episodes of embolism and the duration of AF, as shown in the algorithm (modified from Wipf and Lipsky[44]; published with permission of the *Archives of Internal Medicine*). PT = prothrombin time

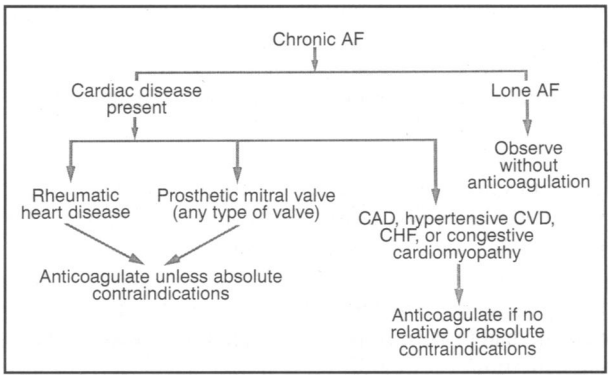

Figure 5.—Therapy for established atrial fibrillation (AF) and recommendations for anticoagulation depend on the associated medical conditions (modified from Wipf and Lipsky[44]; published with permission of the *Archives of Internal Medicine*). CAD = coronary artery disease, CHF = congestive heart failure, CVD = cardiovascular disease

hemorrhagic diathesis; neurosurgical therapy within the past six weeks; recent major trauma; persistently uncontrolled hypertension with diastolic pressures over 105 mm of mercury; a gastrointestinal lesion with recurrent bleeding; and active bleeding from the gastrointestinal, genitourinary, or respiratory tracts. Relative contraindications to anticoagulation include a history of hemorrhage, substantial renal or hepatic disease, active alcoholism, those at risk for falls, a history of noncompliance, or an inability to carefully monitor the patient.

Warfarin therapy is required short term before and after cardioversion unless a patient is hemodynamically unstable or has been in atrial fibrillation less than 48 hours. Patients should be on warfarin therapy with a therapeutic PT INR range of 2.0 to 3.0 a day for three weeks before cardioversion, and warfarin therapy should be continued for a month or two after cardioversion. If cardioversion is unsuccessful or atrial fibrillation recurs soon after, patients should be evaluated for long-term anticoagulation or to repeat the cardioversion.

Warfarin anticoagulation is strongly indicated for patients with atrial fibrillation associated with rheumatic heart disease, prosthetic mitral valves of any type, or a previous embolism (stroke or transient ischemic attack). In the absence of any contraindications, warfarin therapy is indicated for patients with atrial fibrillation with a known cardiac thrombus or with associated nonvalvular cardiac disease, including coronary artery disease, congestive heart failure, cardiomyopathy, and hypertension. Patients older than 75 years with atrial fibrillation may have an increased risk of substantial bleeding on warfarin therapy with a higher intensity of anticoagulation, even when closely monitored, as in the SPAF II trial. Because several other studies have shown benefit and safety of the use of warfarin in the elderly at a lower intensity of anticoagulation (INR 2.0 to 3.0), warfarin use should be considered in this age group, because they are at a particularly high risk of stroke. Aspirin use is indicated for persons with atrial fibrillation who are poor candidates for warfarin therapy because of risk factors for bleeding. Anticoagulation is not recommended for patients younger than 60 with lone atrial fibrillation or for those with pure atrial flutter, which carries a low risk of thromboembolism.

Because the thromboembolic risk of paroxysmal atrial fibrillation in nonvalvular heart disease is greater than for sinus controls, anticoagulation should be considered.

Guidelines for Management of Warfarin Therapy

Warfarin therapy requires close monitoring with frequent laboratory PT measurements and a careful review of complications and medication interactions. To initiate warfarin therapy, low starting doses of 2.5 to 5.0 mg daily are associated with fewer bleeding complications than the common practice of 10 mg daily for three days.[50] The prothrombin time should be checked within three to five days of starting warfarin and then weekly until it has become stable. Monitoring should then be done every four to six weeks and the anticoagulation dose adjusted as needed, with a careful review of medications, diet, and bleeding symptoms. Myriad drug interactions can occur with warfarin, many causing unpredictable fluctuations in PT. The physician ordering anticoagulation must ensure appropriate patient follow-up and may work with an anticoagulation clinic, pharmacist, or nurse practitioner for frequent monitoring. Patients must be educated about their indications for warfarin therapy, the need for careful monitoring, and alterations in physical activity to minimize bleeding risk.

Summary

Several issues remain unresolved in the management of atrial fibrillation. The benefit of a lower intensity of anticoagulation of less than an INR of 2.0 is being studied in an ongoing Dutch trial, PATAF, with patients randomly assigned to different intensities of anticoagulation. The

relative efficacy and safety of warfarin versus aspirin for the primary prevention of stroke in patients older than 75 years of age is controversial. The safety of antiarrhythmic drugs to maintain sinus rhythm has not been directly compared with that of long-term anticoagulation for atrial fibrillation.

Returning to questions asked about the clinical case presented, the cause of atrial fibrillation was nonvalvular heart disease, with a risk of thromboembolism of 5% per year. Whether the patient should have received electrical cardioversion is debatable. He tolerated the arrhythmia well and had prolonged pauses on quinidine therapy. Other antiarrhythmics for cardioversion may have been considered, but with concern about their increased mortality risk, long-term anticoagulation for chronic atrial fibrillation is a reasonable alternative. The development of an embolic event on warfarin therapy appears to be related to inadequate anticoagulation with an INR of 1.4. In the future, this person should benefit from resumed warfarin treatment that aims for an INR in the range of 2.5 to 3.5.

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